Multilayered specification of the T-cell lineage fate.

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Public Summary:
The best-known type of development from stem cells in normal mammals is the production of different types of blood cells. Not only red blood cells but also all the different types of immune cells and defensive cells in the blood share a common stem-cell origin, and all these cell types are continuously produced from stem cells throughout life. Stem cell descendants must make a choice of what kind of blood cell they will become, and this article describes the surprisingly complicated sequence of steps the cells go through in deciding whether to develop into the specific kinds of immune cells called T cells. The steps that lead an individual cell to choose a T-cell fate have been dissected now by combinations of genetics, systems biology, cell culture innovations, and genome research. The review describes the way T cell-specific genes begin to be turned on even while the cells are still “hedging their bets” by continuing to express stem-cell genes. These stem-cell associated genes become silent only after the cells get far enough in the T-cell developmental program to turn on an important gene called Bcl11b. The silencing of the stem-cell associated genes is a crucial step, newly appreciated, that is needed to make the decision to be a T cell irreversible.

Scientific Abstract:
T-cell development from stem cells has provided a highly accessible and detailed view of the regulatory processes that can go into the choice of a cell fate in a postembryonic, stem cell-based system. But it has been a view from the outside. The problems in understanding the regulatory basis for this lineage choice begin with the fact that too many transcription factors are needed to provide crucial input: without any one of them, T-cell development fails. Furthermore, almost all the factors known to provide crucial functions during the climax of T-lineage commitment itself are also vital for earlier functions that establish the pool of multilineage precursors that would normally feed into the T-cell specification process. When the regulatory genes that encode them are mutated, the confounding effects on earlier stages make it difficult to dissect T-cell specification genetically. Yet both the positive and the negative regulatory events involved in the choice of a T-cell fate are actually a mosaic of distinct functions. New evidence has emerged recently that finally provides a way to separate the major components that fit together to drive this process. Here, we review insights into T-cell specification and commitment that emerge from a combination of molecular, cellular, and systems biology approaches. The results reveal the regulatory structure underlying this lineage decision.